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Memory and Attention After Childhood Brain Tumors

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INTRODUCTION

As the survival rates for children with brain tumors have increased, attention has been directed to treatment-related sequelae and their effects on quality of life [1,2]. Follow-up studies of children treated for brain tumors often depend on length of survival or global indices of quality of life as core outcome measures [3,4]: More recent studies have included measures of cognitive function as part of the assessment of long-term morbidity after childhood brain tumors.

Cognitive morbidity after childhood brain tumors has been shown to vary with factors in the child (e.g., age at onset, type and duration of presenting symptoms), tumor type and location, perioperative factors (e.g., hydrocephalus), adjuvant radiation and chemotherapy treatment, and time since treatment [1,2,5]. However, many questions remain unanswered about cognitive morbidity in this population.

AVAILABLE KNOWLEDGE VERSUS HOW KNOWLEDGE IS ACQUIRED

For the most part, studies of the cognitive sequelae of childhood brain tumors have concerned *knowledge availability*. For example, the Information subtest of the Wechsler intelligence scale requires the child to retrieve information about everyday physics, geography, science, and literary culture from long-term memory. Most reports of cognitive morbidity are based on measures of available knowledge in domains such as general information, vocabulary, social comprehension, and academic achievements [6–12].

Memory and attention are the central processes by which knowledge is acquired. In the process of establishing knowledge, we must be awake, aroused, and attentive, able to select among inputs and to remember information actively and prospectively. Information processed in this way has the potential to encode as a long-term memory and, thus, to become part of an individual's established knowledge. Although memory and attention deficits often are described as part of the cognitive morbidity of childhood brain tumors [2], relatively little effort has been directed toward understanding *how childhood brain tumors influence the acquisition of knowledge*.

ATTENTION AND MEMORY IN CHILDREN TREATED FOR BRAIN TUMORS

Attention is an important regulator of cognitive activity that has to do with selection of stimuli for conscious awareness. It involves selecting among competing inputs, so that a response is biased toward one set of elements rather than another. Attention is important, because conscious information is more amenable to change and learning.

The attention skills of children with posterior fossa tumors are of particular interest, because the ascending reticular activating system travels through the brainstem and, together with thalamic and cortical mechanisms, modulates arousal, alertness, and attention [13]. Children with tumors in various brain locations exhibit some attention problems whether or not adjuvant radiation has been part of their treatment [14]. More particularly, children with posterior fossa tumors (medulloblastoma or astrocytoma) performed more poorly than sibling/cousin controls on clinical attention tasks, even though they produced as many correct responses as controls on simple and choice reaction-time tasks, possibly due to the proximity of the lesion to the brainstem ascending activating system [15]. At present, it is not clear whether the number of correct responses is due to a tendency to respond to any signal or whether children with posterior fossa tumors and controls are equally able to respond to targets and to inhibit responses to nontargets.

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Memory

For the most part, studies assessing memory after treatment for a childhood brain tumor assess only explicit recall or recognition memory [16,10,17]. These measures require the conscious, retrospective recall of previously stored information. Significant deficits in auditory verbal memory were evident in half of a sample of children that received radiotherapy for malignant tumors of the posterior fossa or third ventricle [17]. In a group of children with various types of tumors, serial assessments of memory showed declines in half of the children who were radiated before 6 years of age [10]. Of 27 children who were treated surgically for craniopharyngioma, half had some form of memory impairment (immediate or delayed, verbal or nonverbal) [16]. Children with temporal lobe tumors demonstrated verbal or nonverbal memory deficits [18,19].

Despite the results from these studies, the nature of memory and attention deficits is not fully understood. Important questions about attention are unclear; for example, whether distraction interferes more with attention in a tumor group and which tumor types and locations are especially disruptive of attention. Global measures of memory, rather than more specific tests of memory processes, have been used often. Memory and attention often are assessed conjointly with other skills, so how these functions are related is not clear; for example, memory and attention deficits are sometimes inferred from poor performance on tests of general information. The risk of impaired memory and attention has not been ascertained for different tumor types or adjuvant treatments. For a range of cognitive functions, research studies have documented declines over time associated with such factors as age at treatment, adjuvant radiation therapy, and tumor location, but it is not clear how these factors operate in attaining knowledge.

Reciprocal Relations Between Knowledge and Knowledge Acquisition

The relation between the mastery of knowledge and how knowledge is acquired is important and reciprocal. Cognitive development studies have emphasized the interrelations of established knowledge and academic attainments. To learn information, we must attend and remember; reciprocally, domain knowledge is a determinant of how well new information is attended to, learned, and remembered [20,21]. Domain knowledge provides a framework within which to embed new knowledge.

These findings have implications for children with brain tumors. We suggest that some well-documented cognitive deficits in children with brain tumors may be related to deficiencies in basic processes by which knowledge is acquired, including attention and memory. Attention and memory deficits limit the amount of available knowledge; a limited information base, in turn, makes it more difficult to accrue new knowledge. Intact attention and memory allow for the accumulations of knowledge that are reflected later in intelligence and academic achievement scores. If attention or memory is impaired as a result of childhood brain tumors or their adjuvant treatments, then there will be limitations in the acquisition of knowledge and, thus, lower age-adjusted scores on standardized tests of information or general knowledge.

Many research studies show that brain tumors and their treatment are likely to limit the child's established base of knowledge. What needs to be better understood is how the brain tumors and their treatment affect the processes by which knowledge is established.

ATTENTION AND MEMORY PROCESSES

Attention and memory are not unitary constructs, despite the traditional view of memory as a single mental capacity. Recent research has demonstrated the existence of several forms of memory with different processing capacities. We know little about these characteristics in children with brain tumors.

Therefore, it is important to study which aspects of attention and memory might be affected by childhood brain tumors and, in addition, to understand some of the child and tumor variables that increase the risk of subsequent impairment in these processes. To that end, we studied three different processes that are thought to be important for the establishment of knowledge: sustained attention and the ability to withstand distraction, working memory, and implicit memory. In the analysis of each process, we considered child factors (age at diagnosis, time since treatment) and the tumor factors (tumor type and location, treatment with radiation and chemotherapy) that contribute to the risk of subsequent impairment in the processes under study.

Focused and Selective Attention

Attention is a construct in neuropsychology that may be operationalized in tasks that require particular cognitive capacities, such as alertness, focused attention, divided attention, sustained attention, and supervisory attentional control or selective attention [22]. We will be concerned here with focused and selective attention. Focused attention, or vigilance, is the ability to monitor information over time. Selective attention is the ability to maintain vigilance over time while filtering or ignoring distracting information. The analysis of focused and selective attention in children treated for third- and fourth-ventricle tumors will provide information about the long-term effects of tumors in these locations on two important aspects of attention.

Working Memory

The term *working memory* refers to the ‘‘online’’ maintenance of information while it is being processed: the constant updating of incoming information so that processing can be accomplished, and decisions can be made. Working memory is a system for concurrent storage and manipulation of the information necessary to perform mental tasks. An example is holding a telephone number in memory while dialing it. Whereas the older idea of short-term memory involved the passive store of retrospective information, working memory involves the active processing of incoming information and the prospective updating of that information.

Working memory capacity affects success in a variety of cognitive tasks, so deficits in working memory will produce problems in other domains, such as reading, computation, and comprehension. Intact working memory contributes to the maintenance of incoming information, so that it can be placed in a memory store and, over time, become part of the individual’s established knowledge.

In previous work with childhood brain tumors [23,24], we have shown that working memory is disrupted by tumor or surgical damage to structures in the limbic system and the hypothalamic-pituitary axis but not by damage to many other cortical and subcortical structures. Here, we consider working memory in a larger sample of third- and fourth-ventricle tumors to provide information about long-term effects of these conditions on ongoing, prospective memory.

Implicit Memory

The term *memory* is commonly understood to mean conscious recollection of previously experienced or learned information, but past experiences and exposures to events can also influence present memory without awareness or voluntary control. This phenomenon is called *implicit memory*. Implicit memory may be left intact, even when explicit memory is affected profoundly by brain injury. Unlike explicit memory, which depends on conscious attention to the information to be recalled, implicit memory can operate without full attention. Implicit memory is assessed by cognitive tasks measuring the facilitative effects of prior experience without requiring their conscious recollection [25]. Even though children remember more effectively as they grow older, not all components of memory develop at a similar rate, and explicit and implicit memory have different time courses [26–28].

To date, nothing appears to have been documented about the effects of childhood brain tumors or their treatment on implicit memory. The status of both explicit and implicit memory in children with brain tumors has important implications for academic and cognitive remediation; in addition, information about implicit and explicit memory in these children would be relevant to understanding the interaction between attention and memory.

TABLE I. Tumor Type and Location

Third-ventricle tumors
Hypothalamic region
Hypothalamic astrocytoma
Hypothalamic germinoma
Chiasm region
Craniopharyngioma
Optic glioma
Pineal region
Pineal astrocytoma
Pineal germinoma
Thalamus
Thalamic astrocytoma
Thalamic cyst
Fourth-ventricle tumors
Cerebellum
Medulloblastoma
Astrocytoma
Intraventricular
Dermoid

THREE STUDIES

In this paper, we focus on how children with brain tumors attend to and remember simple information that is part of their knowledge base. The children in the study sample had common childhood brain tumors that were located around the third and fourth ventricles (Table I).

FOCUSED AND SELECTIVE ATTENTION

Materials and Methods

Subjects. The study sample consisted of 31 children and adolescents (9 female) with treated brain tumors (17 third-ventricle location, 14 fourth-ventricle location; 12 radiated, 21 nonradiated). Tumor-related symptoms began in middle childhood [mean age at symptom onset 7.0 years; standard deviation (SD) 4.0], and neuropsychological testing occurred well into the chronic phase of recovery (mean time since tumor treatment 4.8 years; SD 2.9). A standard test of intelligence [29,30] was administered, and subjects were selected for scores over 70 on verbal IQ, performance IQ, or both. Intelligence test scores for the group were in the normal range (mean verbal IQ 95.8, SD 13.4; mean performance IQ 91.1, SD 14.9).

Tasks. Each subject was administered two tasks from the Gordon Diagnostic System (GDS) [31,32], which is a portable electronic device with a microprocessor that generates attention tasks and records qualitative and quantitative measures of performance over time. Focused attention or vigilance was measured by using the 9-minute GDS vigilance task. An electronic display flashes

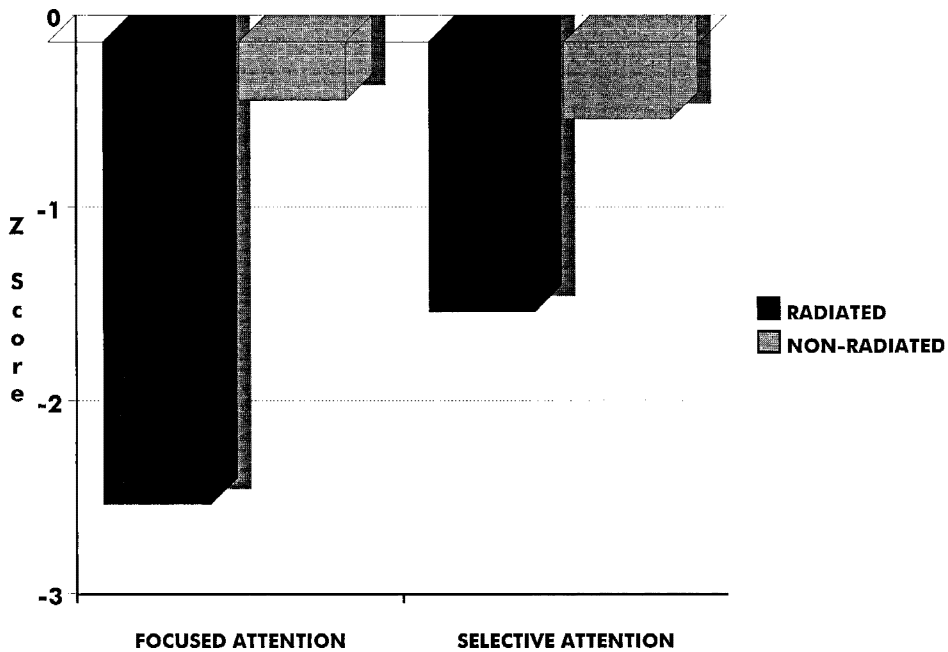

Fig. 1. Focused and selective attention as a function of radiation.

a series of digits in the central column of the computer screen at the rate of one per second. The stimulus is presented for 800 msec, with a 200-msec interval between stimuli. The subject is required to press a button every time the alerting stimulus, 1, is followed by the target, 9, and also to inhibit responding to the alerting stimulus, to nontarget numbers that follow the alerting stimulus, and to target numbers that are not preceded by the alerting cue. A *focused-attention accuracy index* was calculated as follows: number of correct responses, minus number of commission errors (responses to stimuli other than valid targets), divided by number of possible correct responses. The index was converted to a Z score by using supplementary normative data.

Selective attention was measured by using the GDS distractibility task, which is identical to the vigilance task with the addition of distraction in the form of random digits flashing at random intervals on the left and right sides of the central positions of the electronic display. The subject still must press the button every time a 1 is followed by a 9 in the center while ignoring the digits in the outer columns of the display. A *selective-attention accuracy index* was calculated as follows: number of correct responses, minus number of commission errors (responses to stimuli other than valid targets), divided by number of possible correct responses. The index was then converted to a Z score by using supplementary normative data.

Results

The tumor sample showed poor focused attention. The focused-attention accuracy index for the sample, −1.1, was between 1.0 and 1.5 standard deviations below the expected mean of zero but ranged widely (SD 3.1; range from −13.5 to 1.2). The selective-attention accuracy index score, −0.80, was within 1 standard deviation of the mean but also ranged widely (SD 1.7; range from −6.2 to 1.1).

A repeated-measures analysis of variance (ANOVA) for the accuracy scores by condition, tumor location, and radiation showed no interaction and no effect of condition but did show a trend for a radiation effect [$F(1,27) = 3.3$; $P = 0.082$]. Accordingly, we pooled the data across conditions, which revealed the significant effect of radiation [$F(1,29) = 4.2$; $P = 0.049$]. Figure 1 shows that tumor subjects who were treated with radiation performed more poorly than those without radiation on both focused- and selective-attention tasks.

Age at onset and time since treatment, as expected, were correlated with one another. Later age at onset of tumor symptoms was correlated with higher selective-attention scores [$r(30) = -0.41$; $P = 0.022$]. Shorter time since treatment was correlated with higher focused-attention scores [$r(30) = -0.36$; $P = 0.044$] and higher selective-attention scores [$r(30) = -0.44$; $P = 0.014$].

WORKING MEMORY
Materials and Methods

Subjects. The study sample consisted of 64 children and adolescents (25 female) with treated brain tumors (46 third-ventricle location: 30 craniopharyngiomas, 7 anterior third ventricle, 9 posterior third ventricle; 18

fourth-ventricle location: 26 radiated, 38 nonradiated). Tumor-related symptoms began in middle childhood (mean age at onset 8.3 years; SD 3.9), and neuropsychological testing occurred well into the chronic phase of tumor recovery (mean time since tumor treatment 5.9 years; SD 4.5). A standard test of intelligence [29,30] was administered, and subjects were selected with scores above 70 for either or both verbal IQ or performance IQ. Intelligence scores for the group were within the normal range (mean verbal IQ 97.4, SD 13.8; mean performance IQ 87.5, SD 18.8).

Task. Each subject was administered a recognition memory task [33] that involved judgments about the prior occurrence of target words. Subjects were required to indicate whether they had heard each word on a list earlier.

The test consisted of 110 words that were divided into five blocks of 22 words each. The words were drawn randomly from a pool of 1,200 words that were prepared for use in memory research and were selected on the basis of familiarity, concreteness, common length, and syllable structure. The test proper was preceded by a training session that introduced the task and provided some practice. The words in the test were presented by prerecorded tape. Each word occurred twice within a word list: No word occurred on more than one list. The separation of first and second presentations of a word ranged from no intervening words (during a 3-second period) to eight intervening words (during a 24-second period). The subject was asked to respond to each word by indicating whether or not it had been heard previously on the list.

The task required the subject to retain incoming information over periods from 3 seconds to 24 seconds, to perform a simple computational operation comparing new information with old information; and to remember the updated memory register. The active and prospective features qualify the task as one of working memory.

Scores are adjusted for age. Each score from a tumor subject is compared with those of normally developed individuals of the same age. Age percentiles permit comparison of scores among tumor subjects of different ages.

Results

Many individuals in the tumor sample showed poor working memory. Although the mean percentile for the sample, 38.4, was within the normal range, scores ranged over the full scale (SD 32.6; range from 1 to 96), and 41% of the sample scored in the lowest quarter of the distribution.

An ANOVA for the working-memory scores by both tumor location (craniopharyngioma, anterior third ventricle, posterior third ventricle, fourth ventricle) and radiation showed no effect of location but showed a significant main effect of radiation [$F(1,56) = 7.2$; $P = 0.010$] that was qualified by a significant location by radiation interaction [$F(3,56) = 3.0$; $P = 0.038$]. Analysis of the simple main effects in the interaction showed that the radiation effect was more pronounced in the posterior third-ventricle group [$F(1,56) = 10.2$; $P = 0.002$] and was present to some extent in the fourth-ventricle group [$F(1,56) = 3.2$; $P = 0.079$]. Radiation did not influence performance in the craniopharyngioma or anterior third-ventricle groups. Figure 2 shows that radiated subjects with tumors in the other two locations performed poorly on the working-memory task in relation to nonradiated subjects with the same tumor location (fourth-ventricle group) or in relation to both nonradiated peers and age expectations (posterior third-ventricle group). Age at onset and time since treatment, as expected, were correlated with one another. Neither age at onset of tumor symptoms nor time since treatment was correlated with working memory.

IMPLICIT MEMORY
Materials and Methods

Subjects. The study sample consisted of 15 children and adolescents with treated brain tumors of the third ventricle or brainstem (9 radiated) and 15 age- and sex-matched control subjects. Each tumor subject had participated in one or both of the previous studies.

Task. Fragmented picture paradigms have been used previously to measure perceptual priming [34]. The subject is shown a degraded picture of an object. If the object is not identified, then a graded sequence of increasingly more complete versions is presented until identification is successful. In the study phase, subjects attempt to identify fragmented pictures that are presented by an ascending method of limits until identification is successful. In the test phase, an identical procedure is used with all of the old (''primed'') stimuli interspersed with an equal number of new stimuli. The difference between the levels at which the old and new stimuli are identified during the test phase, priming, is a measure of implicit memory. Explicit memory is measured by yes/no recognition of each item during the test phase.

Each subject was administered a set of fragmented picture stimuli (FRAGPIX) on a computer screen. The pictures were chosen from among 260 items [34] that were selected to be high frequency, acquired early in development, and named easily. For each item, eight levels of fragmentation were derived from a pixel-deletion procedure [34]. Progressively more complete versions of the pictures were presented until the item was named. Naming activated a voice key to record reaction time and fragmentation level. In the study phase, 16 fragmented pictures were presented for naming. Thirty-two pictures were named in the test phase 1 hour later (16 original or primed pictures interspersed with 16 new pictures). After

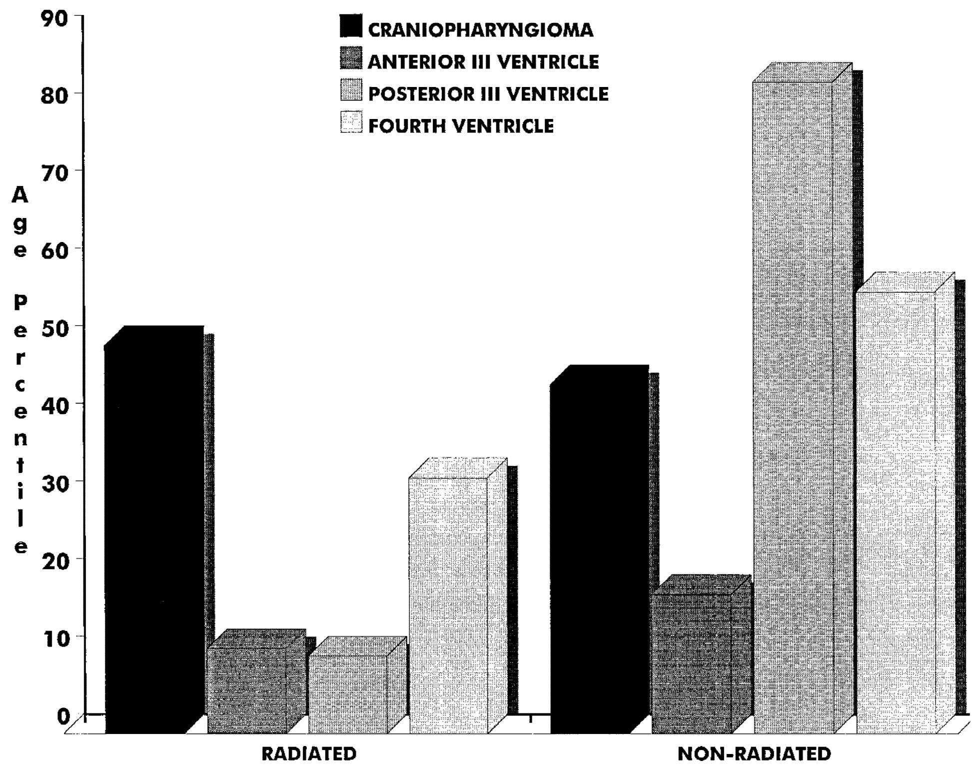

Fig. 2. Working memory as a function of radiation and tumor location.

each correct identification, the child was asked whether or not the item had been seen in the earlier session.

Measures for the first 16 stimuli in the test phase (half of which were primed, and half were unprimed) were completed in a full-attention condition, whereas measures for the remaining 16 stimuli were completed under a divided-attention condition. In the full-attention condition, the children wore light-weight earphones without any transmitted sound. In the divided-attention condition, the children performed the picture-naming task while listening for intelligible words in a tape of ''cafeteria'' noise that had been amplitude-compressed and recorded backward.

Implicit memory, or *priming,* was measured by comparing test items that were presented during the study phase relative to test items that had not been encountered previously. *Explicit memory* was measured under both full and divided attention by using a yes/no recognition of items that had been presented in the test phase.

Results

Both tumor and control groups had a high level of explicit recognition, perhaps reflecting the relatively short (1 hour) time interval between study and test. Even so, the tumor group showed perfect, explicit recognition less often than the control group under conditions of divided (but not full) attention ($\chi^2 = 4.6$; $P = 0.032$). A group (tumor versus control), by attention (full versus divided) repeated-measures ANOVA for the implicit-memory scores, showed a significant main effect of group [$F(1,28) = 4.5$; $P = 0.043$]. Figure 3 shows that tumor subjects showed less priming than controls when they were tested under either full or divided attention. There was no correlation between age at test and memory measures.

DISCUSSION

Memory and attention are faculties that enhance processing in many cognitive domains that are important for learning and for everyday function. Memory and attention are vulnerable to childhood brain tumors of the third and fourth ventricles. Children in these studies were selected to have at least one IQ score above the traditional mental retardation cut-off point of 70, and the group IQ means were within 1 standard deviation of the population mean, so poor attention and memory occur in children with otherwise preserved intelligence.

Tumors that require adjuvant radiation are more likely to result in impaired working memory. For the most part, tumor location considered alone was not a predictor of attention or memory. For example, attention deficits were equally apparent in children treated for third- and fourth-ventricle tumors, which is consistent with the idea that the mechanisms of attention involve multiply distributed neural sites. Combined effects of tumor location

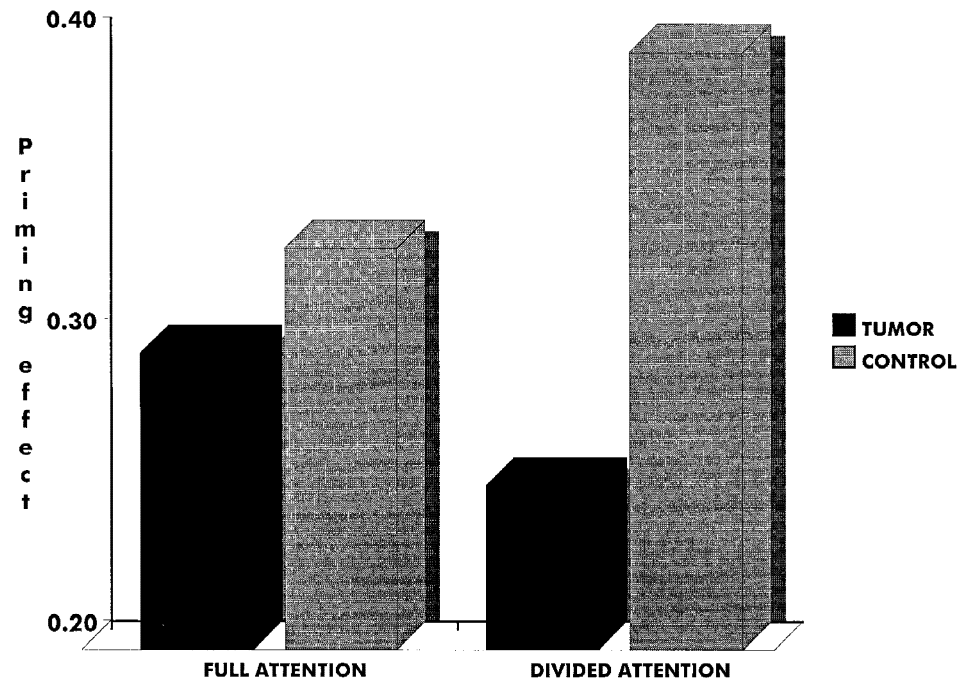

Fig. 3. Implicit memory as a function of group and attention condition.

and treatment history did occur; for example, a history of radiated, posterior third-ventricle tumor debilitated working memory. It should be noted here that tumor location was identified on the basis of the primary tumor site. In future studies, it will be important to analyze tumor damage, not just tumor location, on the basis of detailed neuroimaging analyses.

Attention Resources

Focused and selective attention deficits are common in this sample of children with brain tumors. However, unlike other groups with brain insults acquired during childhood, such as head injury [35], the principal difficulty concerns focused attention or vigilance rather than selective attention.

The main finding is that it is not the presence of a tumor as such that appears to place the child at risk for poor attention but, rather, the combination of a tumor and adjuvant radiation treatment. Many individuals in the clinical sample performed within normal limits on the attention tasks; however, adjuvant radiation treatment was associated with poor attention.

Congruent with several studies indicating the greater cognitive morbidity of younger treated rather than older treated children with brain tumors [2,5], a younger age at tumor onset is more debilitating of focused attention than a later age. For both focused and selective attention, deficits appear to compound with time, which is important in view of observations that the academic impairments of children with treated brain tumors become more apparent with increased time since treatment. However, because the two factors are correlated, it is not clear at present whether age at onset of tumor symptoms or time since treatment is more relevant to the long-term status of focused attention.

Attention and Activation

Increasing attentional demands in the study sample had the paradoxical effect of slightly improving performance. Figure 1 shows that the demands of selective attention were associated with better, not worse, performance in children with radiated brain tumors. In this context, it has been suggested that strong motivational activation improves attention in children with posterior fossa tumors [15]. The relation between attention performance and level of activation in childhood brain tumor survivors is an important issue that warrants more explicit investigation.

Relations Between Attention and Memory

Limitations on attention resources and deficits in working memory, an explicit and intentional use of memory, each occurred in the study sample. Although the relation remains to be tested directly, it is likely that limited attention and poor working memory are causally related. It is of interest that an attention manipulation did not affect implicit memory; that is, reducing the attention available at testing affected explicit but not implicit memory. In neurologically intact adults, reducing the amount of attention available at learning affects forms of

memory that involve conscious recollection more than those that do not require conscious learning [36,37]. This suggests that the retrieval of implicitly acquired perceptual information does not require significant attentional resources.

It would be premature, however, to argue that all forms of implicit memory are unaffected by attention manipulations. Whereas our implicit memory is perceptually driven (it involves clarifying the physical features of fragmented pictures), other implicit-memory tasks are conceptually driven, that is, they involve attending to the meaning of the information. Different brain mechanisms may underlie these forms of implicit memory [38]. It is possible that divided attention at testing may be more relevant to the conceptual implicit-memory tasks for children with brain tumors, just as in head-injured adults, who show normal perceptually driven priming but impaired conceptual priming [36].

Although children with tumors demonstrated a priming effect, the magnitude was less than in controls under either full or divided attention. This means that they benefit less from exposure to material, even material to which they do not attend consciously. The environment in which we learn and remember affords opportunities for implicit learning, which is valuable in a number of ways. Information that is learned implicitly may serve as retrieval cues for explicit recall and recognition. Limitations in the ability to benefit from context and event characteristics that are encoded implicitly, thus, may be part of the memory limitations of children with treated brain tumors.

Typically, traditional cognitive rehabilitation is directed at improving explicit, attended information. Children with these brain tumors may benefit from programs geared toward enhancing their ability not only to recall explicit information but to benefit more fully from repeated exposures to ambient or incidental learning.

CONCLUSIONS AND FUTURE DIRECTIONS

Attention and memory deficits are common in a study sample of children and adolescents with third- and fourth-ventricle tumors. Nevertheless, the risks of these forms of cognitive deficit are not equal for all survivors of third- and fourth-ventricle tumors. Also, some risks appear to be conditional and depend on an interaction between tumor location and treatment history. Because of this, we need larger scale studies to understand the interactions among factors that enhance or reduce the risk of cognitive morbidity. These larger scale studies will be focused most productively by studies that, of necessity, are conducted on a smaller scale that will attempt to clarify the processes by which information is acquired.

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